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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: BIGAZZI
Serial No	: 09/606,569
Confirm. No	: 7698
Filed	: June 29, 2000
For	: USE OF RELAXIN...
Art Unit	: 1647
Examiner	: Regina M. DeBerry
Dated	: January 16, 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST TO CHARGE DEPOSIT ACCOUNT

In the above matter The United States Patent and Trademark Office is hereby requested to charge deposit account 13-0410 as follows:

$165.00 for Filing a brief in support of an appeal under fee code 2402.

Respectfully submitted
for Applicant,

By: _____
John James McGlew
Registration No. 31,903
McGLEW AND TUTTLE, P.C.

JJM:jms
67206RCE.7

DATED: January 16, 2004
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SHOULD ANY OTHER FEE BE REQUIRED, THE PATENT AND TRADEMARK OFFICE IS HEREBY REQUESTED TO CHARGE SUCH FEE TO OUR DEPOSIT ACCOUNT 13-0410.

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS EXPRESS MAIL IN AN ENVELOPE ADDRESSED TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, NO.: EV323629574US.

McGLEW AND TUTTLE, P.C.
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BY: Maria Rouell DATE: January 16, 2004

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01-20-04

Image AF/ 1647

Attorney Docket No. 67206 RCE

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant	: MARIO BIGAZZI
Serial No.	: 09/606,569
Filed	: June 29, 2000
Confirmation No.	: 7698
For	: USE OF RELAXIN FOR STIMULATING THE DEVELOPMENT OF ACTIVATED HUMAN T CELLS INTO TH1-LIKE EFFECTORS
Art Unit	: 1647
Examiner	: Regina M. DeBerry
Dated	: January 16, 2004

Hon. Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

BRIEF ON APPEAL

I - REAL PARTY IN INTEREST

This application is unassigned, and thus appellant (applicant) remains the real party in interest herein.

II - RELATED APPEALS AND INTERFERENCES

Appellant and appellant's legal representative (there being no assignee) have no knowledge of any appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

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III - STATUS OF CLAIMS

Original claims 1-5 stand rejected and are on appeal.

Original claim 6, the only remaining claim, has been withdrawn as directed to a non-elected invention.

No claims have been cancelled or amended.

IV - STATUS OF AMENDMENTS AFTER FINAL REJECTION

No amendment after final rejection has been filed.

V - SUMMARY OF THE INVENTION

This invention concerns new methods of use of the hormone relaxin (RLX) or derivative thereof, involving administering an effective amount of RLX (or derivative) to a human patient:

- for treating a Th2-dominated disease (claim 1);

- for inhibiting a pathogenic Th2 response by inducing endogenous IFN-γ production (claim 2);

- for stimulating the development of activated human T cells into Th1-like effectors for treating a Th2-dominated disease (claim 3);

- for enhancing Th1 response of the immunological system of the patient for treating (relieving) a Th2-dominated disease (claim 4); and

- for inducing endogenous IFN-γ production for treating (relieving) a Th2-dominated disease (claim 5);

(spec., p. 17, line 12, to p. 18, line 2).

$CD4^+$ Th lymphocytes are classified into different functional subsets per their profile of cytokine production, such that Th1 cells produce IFN-γ, IL-2 and TNF-β, while Th2 cells produce IL-4,

IL-5, IL-6, IL-9, IL-10 and IL-13. Development of Th1- or Th2-dominated responses depends on several factors, the most critical being cytokines produced in the micro environment during antigen presentation. IFN-γ, IFN-α and IL-12 promote differentiation of naive Th cells into the Th1 pathway, whereas IL-4 appears to be the most dominant factor for determining Th2 polarization (spec., p. 2, lines 3-19).

It has been found per the present invention that RLX has an effect on differentiation of antigen-specific T cells into IFN-γ-producing and/or IL-4-producing cells, and on production of IFN-γ and IL-4 induced by TCR (i.e., T cell receptor) stimulation of established T cell clones. Experiments show that RLX, when added to PBMC (i.e., peripheral blood mononuclear cell) cultures, favors development of antigen-specific $CD4^+$ T cells into T cells showing enhanced ability to produce IFN-γ, without exerting any effect on IL-4 production. In addition, RLX also increases both IFN-γ mRNA expression and IFN-γ production induced by TCR stimulation of established $CD4^+$ T cell clones, indicating that this hormone can directly influence both the differentiation and function of $CD4^+$ effector T lymphocytes (spec., p. 3, lines 8-19).

[N.b. PBMC stands for peripheral blood mononuclear cell, as is clear from col. 12, lines 20-21, of Kingsbury et al., U.S. Patent 6,323,334, issued November 27, 2001, listed on p. 3 of the April 1, 2002 amendment and discussed on p. 15-17 of the April 23, 2002 supplemental amendment herein].

Tests herein show that the promoting effect of RLX on the development of IFN-γ-producing cells is not due to RLX-induced release of IL-12 and/or IFN-α by antigen-presenting cells (spec., p. 3, line 24, to p. 4, line 2).

In particular, the effect of RLX on the differentiation of antigen-specific T cells into IFN-γ and/or IL-4-producing cells, has been analyzed, as well as on the production of IFN-γ and IL-4 induced by TCR stimulation of established T cell clones. The results show that RLX, when added to cultures of PBMC, favors the development of antigen-specific $CD4^+$ T cells into T cells showing enhanced ability to produce IFN-γ, without exerting any effect on production of IL-4. In addition, RLX also increases both IFN-γ mRNA expression and IFN-γ production induced by TCR stimulation of established $CD4^+$ T cell clones, suggesting that this hormone can directly influence both the differentiation and function of $CD4^+$ effector T lymphocytes (spec., p. 4, lines 3-14).

VI - CONCISE STATEMENT OF ALL ISSUES PRESENTED FOR REVIEW

(Sole Issue) Whether claims 1-5 are unpatentable under 35 USC 103 over Bani et al (Bani) in view of Masini et al (Masini).

VII - GROUPING OF CLAIMS

It is submitted that each of claims 1-5 rejected under 35 USC 103 is separately patentable and that they do not stand or fall together.

VIII - ARGUMENT

Sole Issue

Whether claims 1-5 are unpatentable under 35 USC 103 over Bani et al. in view of Masini et al.:

Bani et al., "Relaxin Counteracts Asthma-Like Reaction Induced by Inhaled Antigen in Sensitized Guinea Pigs," Endocrinology 1997, 138 (5):1909-1915 (i.e., including the five co-authors: D. Bani, L. Ballati, E. Masini, the present inventor M. Bigazzi, and T. Bani-Sacchi), hereinafter "Bani"; and

Masini et al., Abstract, "Relaxin inhibits histamine release from mast cells: involvement of nitric oxide production," Inflammation Research Apr. 1995, 44 Suppl 1:S12-13 (i.e., including the six co-authors E. Masini, M. G. DiBello, D. Bani, the present inventor M. Bigazzi, T. Bani-Sacchi, and P. F. Mannaioni), hereinafter "Masini".

Applicant retains for the record the following two additional references:

Cronin et al., U.S. Patent 5,166,191, issued November 24, 1992, hereinafter "Cronin;" and

Bigazzi, U.S. Patent 5,952,296, issued September 14, 1999 to the present inventor, appellant herein (regarding which a terminal disclaimer has been filed herein), hereinafter "Bigazzi-296."

The Final Rejection (p. 3-4) generally holds that the art cited, i.e., Bani in view of Masini, teaches a species of the generic claims herein, in that it is known that asthma is a Th2-dominated disease whereupon the species asthma anticipates the

claimed genus (Th2 dominated disease, pathogenic Th2 response), because the references teach the exact same method step (administering RLX in a "subject" exhibiting a Th2-dominated disease or pathogenic Th2 response); the only difference is the instant claims are drawn to humans.

However, the Examiner discounts this difference by asserting:

Point (1) - that guinea pigs per Bani are proper models, and further holds

Point (2) - that the mechanism by which you get relief of disease is not relevant because it inherently happens,

Point (3) - that the claims fail to distinguish from the referenced patient population, and

Point (4) - that scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Masini is earlier (1995) than Bani (1997), and both have four common co-authors: Bani, Masini, Bigazzi (appellant herein), and Bani-Sacchi (Masini also having DiBello and Mannaioni as co-authors, and Bani also having Ballati as a co-author).

Masini (Abstract) notes that RLX inhibited histamine release from isolated rat serosal mast cells, and stimulated NO (nitric oxide) production, whereas NG-monomethyl-L-arginine antagonized RLX-induced inhibition of histamine release, thereby showing that the inhibiting effect of RLX on histamine release involved endogenous NO production.

Masini thus concludes that RLX-induced vasodilation seems dependent, at least in part, on local NO production by mast cells

and raises the possibility that RLX or RLX-derived drugs may be used to treat allergic and peripheral vascular diseases.

Two years later, necessarily mindful of their earlier work per Masini, the co-authors per Bani state (see Bani, Abstract) that RLX reduces the severity of respiratory abnormalities in ovalbumin pre-sensitized guinea pigs exposed to ovalbumin aerosol, and promotes dilation of alveolar blood capillaries and reduces the thickness of the air-blood barrier, thus providing evidence for an anti asthmatic property of RLX and raising the possibility of new therapeutic strategies for allergic asthma in humans.

Bani notes (see Bani, Discussion, p. 8, second complete par.) that in previous studies, RLX has been demonstrated to evoke the response of its targets through stimulation of endogenous NO production, NO being shown to exert beneficial effects on asthma, such that the anti asthmatic properties of RLX may also rely on its ability to stimulate NO production by cells in the lungs.

Despite the Masini conclusion that the rat cell based dependency of RLX-induced vasodilation on NO production raises the possibility that RLX or RLX-derived drugs may be used to treat allergic and peripheral vascular diseases, the Bani finding (that RLX reduces respiratory abnormalities in guinea pigs and promotes dilation of alveolar blood capillaries and reduces the thickness of the air-blood barrier, thereby providing evidence for an anti asthmatic property of RLX), still only leads Bani to regard the results as raising the possibility of new therapeutic strategies for allergic asthma in humans.

At the outset, given the concept that asthma is a species of a Th2-dominated disease genus, it is clear that the instant invention concerns treating asthma in human beings, not in rats (Masini) or guinea pigs (Bani).

Masini only indicates that RLX acts by causing endogenous NO production to inhibit histamine release, in rat cell based tests, and it is only on the basis of NO production that RLX is thought to raise the possibility of use to treat allergic diseases.

Such Masini assertion is not motivation to carry out the present invention with an expectation of success (see p. 5 of November 4, 2002 Office Action), but rather a speculative invitation to experiment in the empirical and unpredictable medical arts.

Bani only shows that RLX has an anti asthmatic property in treating ovalbumin pre-sensitized guinea pigs, similarly to Masini, i.e., by endogenous production of NO which has been shown to exert beneficial effects on asthma, and thus likewise it is mainly on the basis of NO production that RLX is thought to raise the possibility of use to treat asthma.

Here, also, such Bani assertion is not motivation to carry out the present invention with an expectation of success (see p. 5 of November 4, 2002 Office Action), but rather a speculative invitation to experiment in the empirical and unpredictable medical arts.

Nothing is said in Masini and/or Bani that teaches that RLX is useful to treat asthma in human beings. At best, despite any Examiner asserted art-based motivation to the skilled artisan to combine these two references, Masini and Bani present the classic

situation that in view of the suggested use of RLX to treat allergic diseases (Masini) and to counteract allergic asthma in guinea pigs (Bani), expressly thought in each of the two references to involve endogenous NO production, it would be obvious to try use of RLX to treat asthma with respect to human beings, in order to determine whether it is effective for human use or not.

An invention must be obvious over the art per se, in the sense of 35 USC 103, without having to try in order to determine whether the result is successful or unsuccessful. There is no art taught equivalency between rat and/or guinea pig based RLX experiments and human based RLX experiments in general, or in particular regard to endogenous NO production, on the one hand, and TH1 cell production as opposed to Th2 cell production, on the other hand.

Indeed, the applied art is based on efforts of appellant herein with co-authors and any personal knowledge of appellant herein may not be imputed to the art. More significant, it is clear from Masini and Bani that the various co-authors therein in reality represent the skilled artisan in this field of endeavor, i.e., the unpredictable medical arts, where empirical tests are required to establish useful advances, and where speculation as to mechanisms of action or possible medical uses cannot be accepted in place of empirical test results.

Thus, these co-authors as skilled artisan do not say that rat derived cell tests (Masini) and guinea pig tests (Bani) teach that RLX is useful to treat asthma in human beings, but rather that the Masini test results of rat cell based dependency of RLX-induced

vasodilation on NO production raises the possibility that RLX or RLX-derived drugs may be used to treat allergic and peripheral vascular diseases, and likewise that the Bani guinea pig test results that RLX reduces respiratory abnormalities and promotes dilation of alveolar blood capillaries and reduces the thickness of the air-blood barrier, provides evidence for an anti asthmatic property of RLX, thus similarly raising the possibility of new therapeutic strategies for allergic asthma in humans.

Point (1) - the Examiner's assertion that guinea pigs per Bani are proper models, thus vitiating the difference between the instant use of RLX to treat human beings and the Bani use of RLX in guinea pig tests, is not well taken.

There is no art basis to equate guinea pig based tests as used in Bani, with human cell based tests as used herein. Indeed, both Bani and Masini constitute the work of individuals who comprise skilled artisans in the unpredictable empirical medical field, as noted above, and who do not state, as the Examiner implies, that guinea pig based tests are equivalent to human cell based tests. Instead, Bani and Masini both premise their results on endogenous NO production, which only raises the possibility that RLX may be useful (or may not be useful) for treating human beings.

Point (2) - The Examiner's assertion that the mechanism by which you get relief of disease is not relevant because it inherently happens, is also not well taken.

It is only because of the Bani and Masini proposed RLX-induced endogenous NO production mechanism of action explanation that the possibility is raised that RLX may be useful to treat human beings, not because of the mechanism of action effect of RLX on any Th2-dominated disease as found per the present invention.

This is not a case where the art shows that human cell based tests indicate that endogenous NO production is found and on the basis of which the possibility is raised that RLX may be useful to treat human beings.

It certainly is not the case where the art shows that human cell based tests indicate asthma to be a Th2-dominated disease, and:

- that it is treatable in human patients by RLX (claim 1), or

- that a pathogenic Th2 response is inhibitable in human patients by RLX to induce endogenous IFN-γ production (claim 2), or

- that development of activated human T cells into Th1-like effectors is stimulatable by RLX to treat a Th2-dominated disease in human patients (claim 3), or

- that a Th2-dominated disease is treatable in human patients by RLX to enhance the Th1 response of the immunological system (claim 4), or

- that a Th2-dominated disease is treatable in human patients by RLX to induce endogenous IFN-γ production (claim 5).

Indeed, such is the basis of the present invention itself.

Point (3) - The Examiner's assertion that the claims fail to distinguish from the referenced patient population, is equally not well taken.

The only relevant patient population at issue herein is the human population, and as earlier indicated, no art established equivalency has been set forth by the Examiner as between guinea pigs and human beings (human patients) to support such assertion.

Point (4) - The Examiner's assertion that scientific reasoning and evidence as a whole indicates that the rejection should be maintained, is likewise not well taken.

The Examiner has not advanced any scientific reasoning or evidence supporting the art rejection. Instead, it is submitted that the art rejection is inferentially premised on an erroneous "at least try" test of obviousness, rather that the true test that the claimed concept must be obvious without having to try to establish whether success or lack of success is the result.

There is no presumption of obviousness under 35 USC 103. Moreover, the results of the invention cannot be appreciated in a technical vacuum, given the implicit unpredictability of action of RLX in the instant empirical medical arts.

As noted in Cronin, cited in appellant's Bigazzi-296, RLX is difficult to recover in pure form, being generally obtained as a crude aqueous extract from sow corpora lutea, and was only recently obtained as highly purified RLX from the ovaries of pregnant pigs, rats, sharks, and the placentas of horses and rabbits, with

partially purified RLX being obtained from cow and human corpora lutea, placentas and decidua (col. 2, lines 15-35).

Per Cronin, mature human RLX exists in the human in the corpora lutea of pregnancy, in the non-pregnant female and in the male (seminal fluid), yet the obtaining of purified RLX preparations from human corpora lutea, placentas and decidua has not yet been demonstrated (col. 1, lines 8-13 and 49-52). Recombinant techniques have been applied to isolation of cDNA clones for rat and porcine RLX, and two human gene forms have been identified by genomic cloning, although only one such gene form, termed H2 relaxin, has been found to be transcribed in corpora lutea (col. 1, lines 53-68).

Cronin states that RLX consists of two peptide chains, referred to as A and B, joined by disulfide bonds with an intra-chain disulfide loop in the A-chain analogous to that of the hormone insulin, the two human RLX genes showing considerable nucleotide and amino acid sequence homology to each other, but with notable regions of sequence divergence, particularly in the amino-terminal region of both A- and B-chains (col. 3, lines 1-8).

Indeed, Cronin notes that the structure of relaxin has apparently diverged considerably among species during evolution, with only 40-48% amino acid sequence homology existing among porcine, rat, shark and human RLX, yet in all species examined, the primary translation product of H2 RLX is a pre prorelaxin consisting of a 25 amino acid signal sequence followed by a B chain of about 29-33 amino acids, a connecting peptide of 104-107 amino

acids (C peptide), and an A chain of 24 amino acids, with the further processing of the pro hormone obtained into RLX being not entirely understood (col. 3, lines 9-26).

Cronin confirms the art designated definition of "relaxin" as generally including polypeptides comprising the amino acid sequence of a naturally occurring (human or non-human animal, such as porcine, murine, etc.) RLX, or comprising an amino acid sequence which differs from such native RLX amino acid sequences by substitutions, deletions, additions and/or modifications of one or more amino acid residues in the A- and/or B-chains of the respective native RLX, as well as glycosylation variants, unglycosylated forms, organic and inorganic salts, and covalently modified derivatives of such native and modified peptides (col. 8, line 6, to col. 9, line 31; and col. 10, line 10, to col. 12, line 36).

Indeed, Cronin emphasizes the unpredictability as to medical uses of RLX in regard to various therapies there discussed, and the confusing results as to given medical uses that have been obtained therewith (col. 4, line 21, to col. 5, line 29; and col. 17, line 38, to col. 18, line 13).

Bigazzi-296, like Cronin, also confirms that the structure of RLX, which is similar to insulin, is different for each species of animals and has been difficult to obtain in pure form (col. 1, lines 9-36), limiting the value of medical use test results therewith (col. 1, lines 37-40; and col. 2, lines 17-41), and emphasizing the unpredictability of its therapeutic use due to its dose-dependency (col. 8, lines 63-67; and col. 9, lines 19-24).

Hence, there is no art supported basis for concluding that tests on animal derived cells such as guinea pig derived cells per Bani or rat derived cells per Masini are equivalent to human derived cells, or that tests using RLX in one cellular environment (animal subjects) are acceptable to establish predictably corresponding use in another cellular environment (human patients).

Clearly, Bani and Masini are not concerned with the instant methods of treating a Th2-dominated disease in a human patient (claims 1, 4 and 5), inhibiting a pathogenic Th2 response in a human patient (claim 2), or stimulating the development of activated human T cells into Th1-like effectors in a human patient (claim 3), let alone the non-elected method of regulating immune homeostasis during pregnancy in a human female patient (claim 6), based on a different mechanism, i.e., stimulation of Th1-like effectors in humans (spec., p. 3, lines 8-19).

Any motivation of the skilled artisan to combine Bani and Masini would still result only in the speculative raising of the possibility that RLX could be used to treat allergic diseases (Masini) or asthma (Bani) in human beings. This is far different from the Examiner's unsupported position that the combination of Bani and Masini teaches in fact that it is obvious in the sense of 35 USC 103 that RLX is usable to treat asthma in human beings.

This unsupported position of obviousness on the part of the Examiner could only occur by impermissible hindsight use of the instant invention itself to show that it is not an invention.

Clearly, appellant was first to recognize RLX use in humans to treat Th2-dominated diseases, based on appellant's recognition that RLX has an inhibiting effect on pathogenic Th2 response.

Bani and Masini have not enriched the medical arts by providing a new method of treating a Th2-dominated disease or pathogenic Th2 response in a human patient, but rather at best alone or in combination present a speculative invitation to experiment to see whether the raised possibility that RLX may be able to treat asthma in human beings is actually correct or incorrect. On the other hand, the invention herein has enriched the medical arts by providing a new and unobvious therapeutic method empirically useful for treating human patients.

This is a situation dealing with an empirical art, with respect to which the court in In re Tomlinson et al., 150 USPQ 623, 626 (1966), stated (in one long paragraph):

> As we see it, appellant's invention is the discovery of what stabilizers for other materials, known in the art, will, and which will not, stabilize polypropylene against degradation by light. The solicitor asserts that one skilled in the art "would expect an[y] ultraviolet light stabilizer for polyethylene to be effective as an ultraviolet stabilizer in polypropylene"....The examiner, with whom the board expressed "total agreement," did not go that far, saying "it would be obvious for a skilled chemist to try to stabilize polypropylene with a known stabilizer for polyethylene," and that it would be

"routine experimentation" for a skilled chemist to attempt to stabilize polypropylene against the deteriorative effect of light by first trying the known stabilizers for polyethylene such as the nickel and cobalt dialkyldithiocarbamates," citing In re Moreton, 48 CCPA 928, 288 F.2d 940, 129 USPQ 288, for the proposition that obviousness does not require absolute predictability. [Emphasis in original.]

Continuing (in that same long paragraph), the court said:

> Our reply to this view is simply that it begs the question, which is obviousness under section 103 of compositions and methods, not of the direction to be taken in making efforts or attempts. Slight reflection suggests, we think, that there is usually an element of "obvious to try" in any research endeavor, that it is not undertaken with complete blindness but rather with some semblance of a chance of success, and that patentability determinations based on that as the test would not only be contrary to statute but result in a marked deterioration of the entire patent system as an incentive to invest in those efforts and attempts which go by the name of "research." [Emphasis in original.]

The court in Tomlinson further noted (p. 627):

> Considering the evidence as a whole, we think it inescapable that we are here dealing with an art that is quite empirical. [Emphasis added.]

Given the unpredictability of results of efforts in the medical field, and the empirical nature of medical experiments and treatments, as confirmed by Cronin and Bigazzi-296 as noted above, even if the skilled artisan were motivated and had expectations of success, the combination of Bani and Masini represents a speculative invitation to experiment to ascertain whether or not RLX is in fact useful to treat asthma in human patients.

The art rejection under 35 USC 103 is unwarranted since it is based on impermissible hindsight inclusion of the instant disclosure (cf., spec., p. 14, lines 1-12) to show that the instant invention is not an invention, and an implicit holding that on the basis of Bani and Masini it would be obvious to try experiments, i.e., the artisan would be motivated to experiment, to ascertain whether or not RLX is useful to treat asthma in human subjects.

It cannot be overemphasized that the Bani and Masini co-authors, as skilled artisans in the empirical (unpredictable) medical arts, do not teach that it would be obvious to use RLX to treat asthma in human patients, but only that, based rat cell and guinea pig tests, involving attendant endogenous NO production, the possibility is raised that RLX may (or may not) be used to treat allergic diseases (Masini) or that new therapeutic strategies may (or may not) arise for allergic asthma in humans.

For the above reasons, the Board is respectfully requested to reverse the Examiner's sole rejection of appealed claims 1-5 under 35 USC 103, and allow such claims.

Respectfully submitted
for Appellant,

By Peter James Franco

PJF/E

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Dated: January 16, 2004

IF THIS RESPONSE IS CONSIDERED FILED OUTSIDE A SHORTENED STATUTORY PERIOD SET OR NON-STATUTORY PERIOD, THE COMMISSIONER FOR PATENTS IS HEREBY PETITIONED FOR AN EXTENSION OF TIME UNDER 37 CFR 1.136 (a) AND HEREBY AUTHORIZED TO CHARGE THE FEE REQUIRED, FOR THIS RESPONSE TO BE CONSIDERED TIMELY, TO OUR DEPOSIT ACCOUNT NO. 13-0410.

SHOULD ANY OTHER FEE BE REQUIRED, SUCH FEE IS HEREBY REQUESTED TO BE CHARGED TO SAID DEPOSIT ACCOUNT NO. 13-0410.

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS EXPRESS MAIL IN AN ENVELOPE ADDRESSED TO: HON. COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VIRGINIA 22313-1450.

RECEIPT NO. EV323629574US ON January 16, 2004

BY: Maria Harrell
MAIL CLERK

1/16/2004
DATE

IX - APPENDIX

The claims on appeal are original claims 1-5 as follows:

1. (ORIGINAL) Method of treating a Th2-dominated disease in a human patient exhibiting said disease, comprising administering to the patient an effective amount of relaxin or derivative thereof for relieving said disease.

2. (ORIGINAL) Method of inhibiting a pathogenic Th2 response in a human patient exhibiting said pathogenic Th2 response, comprising administering to the patient an effective amount of relaxin or derivative thereof for inducing endogenous IFN-γ production for inhibiting said pathogenic Th2 response.

3. (ORIGINAL) Method of stimulating the development of activated human T cells into Th1-like effectors for treating a Th2-dominated disease in a human patient exhibiting said disease, comprising administering to the patient an effective amount of relaxin or derivative thereof for stimulating said development.

4. (ORIGINAL) Method of treating a Th2-dominated disease in a human patient exhibiting said disease, comprising administering to the patient an effective amount of relaxin or a derivative thereof for enhancing Th1 response of the immunological system of the patient for relieving said disease.

5. (ORIGINAL) Method of treating a Th2-dominated disease in a human patient exhibiting said disease, comprising administering to the patient an effective amount of relaxin or a derivative thereof for inducing endogenous IFN-γ production for relieving said disease.

The only remaining claim in the case is original claim 6, withdrawn as being directed to a non-elected invention, as follows:

6. (WITHDRAWN) Method of regulating immune homeostasis during pregnancy of a human female patient exhibiting imbalance in immune homeostasis, comprising administering to the patient an effective amount of relaxin or a derivative thereof for regulating said immune homeostasis.

OIPE JC67
JAN 16 2004
PATENT & TRADEMARK OFFICE

Attorney Docket No. 67206 RCE

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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Hon. Commissioner for Patents
P.O. Box 1450
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BRIEF ON APPEAL

I - REAL PARTY IN INTEREST

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Appellant and appellant's legal representative (there being no assignee) have no knowledge of any appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

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This invention concerns new methods of use of the hormone relaxin (RLX) or derivative thereof, involving administering an effective amount of RLX (or derivative) to a human patient:

- for treating a Th2-dominated disease (claim 1);

- for inhibiting a pathogenic Th2 response by inducing endogenous IFN-γ production (claim 2);

- for stimulating the development of activated human T cells into Th1-like effectors for treating a Th2-dominated disease (claim 3);

- for enhancing Th1 response of the immunological system of the patient for treating (relieving) a Th2-dominated disease (claim 4); and

- for inducing endogenous IFN-γ production for treating (relieving) a Th2-dominated disease (claim 5);

(spec., p. 17, line 12, to p. 18, line 2).

$CD4^+$ Th lymphocytes are classified into different functional subsets per their profile of cytokine production, such that Th1 cells produce IFN-γ, IL-2 and TNF-β, while Th2 cells produce IL-4,

IL-5, IL-6, IL-9, IL-10 and IL-13. Development of Th1- or Th2-dominated responses depends on several factors, the most critical being cytokines produced in the micro environment during antigen presentation. IFN-γ, IFN-α and IL-12 promote differentiation of naive Th cells into the Th1 pathway, whereas IL-4 appears to be the most dominant factor for determining Th2 polarization (spec., p. 2, lines 3-19).

It has been found per the present invention that RLX has an effect on differentiation of antigen-specific T cells into IFN-γ-producing and/or IL-4-producing cells, and on production of IFN-γ and IL-4 induced by TCR (i.e., T cell receptor) stimulation of established T cell clones. Experiments show that RLX, when added to PBMC (i.e., peripheral blood mononuclear cell) cultures, favors development of antigen-specific $CD4^+$ T cells into T cells showing enhanced ability to produce IFN-γ, without exerting any effect on IL-4 production. In addition, RLX also increases both IFN-γ mRNA expression and IFN-γ production induced by TCR stimulation of established $CD4^+$ T cell clones, indicating that this hormone can directly influence both the differentiation and function of $CD4^+$ effector T lymphocytes (spec., p. 3, lines 8-19).

[N.b. PBMC stands for peripheral blood mononuclear cell, as is clear from col. 12, lines 20-21, of Kingsbury et al., U.S. Patent 6,323,334, issued November 27, 2001, listed on p. 3 of the April 1, 2002 amendment and discussed on p. 15-17 of the April 23, 2002 supplemental amendment herein].

Tests herein show that the promoting effect of RLX on the development of IFN-γ-producing cells is not due to RLX-induced release of IL-12 and/or IFN-α by antigen-presenting cells (spec., p. 3, line 24, to p. 4, line 2).

In particular, the effect of RLX on the differentiation of antigen-specific T cells into IFN-γ and/or IL-4-producing cells, has been analyzed, as well as on the production of IFN-γ and IL-4 induced by TCR stimulation of established T cell clones. The results show that RLX, when added to cultures of PBMC, favors the development of antigen-specific $CD4^+$ T cells into T cells showing enhanced ability to produce IFN-γ, without exerting any effect on production of IL-4. In addition, RLX also increases both IFN-γ mRNA expression and IFN-γ production induced by TCR stimulation of established $CD4^+$ T cell clones, suggesting that this hormone can directly influence both the differentiation and function of $CD4^+$ effector T lymphocytes (spec., p. 4, lines 3-14).

VI - CONCISE STATEMENT OF ALL ISSUES PRESENTED FOR REVIEW

(Sole Issue) Whether claims 1-5 are unpatentable under 35 USC 103 over Bani et al (Bani) in view of Masini et al (Masini).

VII - GROUPING OF CLAIMS

It is submitted that each of claims 1-5 rejected under 35 USC 103 is separately patentable and that they do not stand or fall together.

VIII - ARGUMENT

Sole Issue

Whether claims 1-5 are unpatentable under 35 USC 103 over Bani et al. in view of Masini et al.:

Bani et al., "Relaxin Counteracts Asthma-Like Reaction Induced by Inhaled Antigen in Sensitized Guinea Pigs," Endocrinology 1997, 138 (5):1909-1915 (i.e., including the five co-authors: D. Bani, L. Ballati, E. Masini, the present inventor M. Bigazzi, and T. Bani-Sacchi), hereinafter "Bani"; and

Masini et al., Abstract, "Relaxin inhibits histamine release from mast cells: involvement of nitric oxide production," Inflammation Research Apr. 1995, 44 Suppl 1:S12-13 (i.e., including the six co-authors E. Masini, M. G. DiBello, D. Bani, the present inventor M. Bigazzi, T. Bani-Sacchi, and P. F. Mannaioni), hereinafter "Masini".

Applicant retains for the record the following two additional references:

Cronin et al., U.S. Patent 5,166,191, issued November 24, 1992, hereinafter "Cronin;" and

Bigazzi, U.S. Patent 5,952,296, issued September 14, 1999 to the present inventor, appellant herein (regarding which a terminal disclaimer has been filed herein), hereinafter "Bigazzi-296."

The Final Rejection (p. 3-4) generally holds that the art cited, i.e., Bani in view of Masini, teaches a species of the generic claims herein, in that it is known that asthma is a Th2-dominated disease whereupon the species asthma anticipates the

claimed genus (Th2 dominated disease, pathogenic Th2 response), because the references teach the exact same method step (administering RLX in a "subject" exhibiting a Th2-dominated disease or pathogenic Th2 response); the only difference is the instant claims are drawn to humans.

However, the Examiner discounts this difference by asserting:

Point (1) - that guinea pigs per Bani are proper models, and further holds

Point (2) - that the mechanism by which you get relief of disease is not relevant because it inherently happens,

Point (3) - that the claims fail to distinguish from the referenced patient population, and

Point (4) - that scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Masini is earlier (1995) than Bani (1997), and both have four common co-authors: Bani, Masini, Bigazzi (appellant herein), and Bani-Sacchi (Masini also having DiBello and Mannaioni as co-authors, and Bani also having Ballati as a co-author).

Masini (Abstract) notes that RLX inhibited histamine release from isolated rat serosal mast cells, and stimulated NO (nitric oxide) production, whereas NG-monomethyl-L-arginine antagonized RLX-induced inhibition of histamine release, thereby showing that the inhibiting effect of RLX on histamine release involved endogenous NO production.

Masini thus concludes that RLX-induced vasodilation seems dependent, at least in part, on local NO production by mast cells

and raises the possibility that RLX or RLX-derived drugs may be used to treat allergic and peripheral vascular diseases.

Two years later, necessarily mindful of their earlier work per Masini, the co-authors per Bani state (see Bani, Abstract) that RLX reduces the severity of respiratory abnormalities in ovalbumin pre-sensitized guinea pigs exposed to ovalbumin aerosol, and promotes dilation of alveolar blood capillaries and reduces the thickness of the air-blood barrier, thus providing evidence for an anti asthmatic property of RLX and raising the possibility of new therapeutic strategies for allergic asthma in humans.

Bani notes (see Bani, Discussion, p. 8, second complete par.) that in previous studies, RLX has been demonstrated to evoke the response of its targets through stimulation of endogenous NO production, NO being shown to exert beneficial effects on asthma, such that the anti asthmatic properties of RLX may also rely on its ability to stimulate NO production by cells in the lungs.

Despite the Masini conclusion that the rat cell based dependency of RLX-induced vasodilation on NO production raises the possibility that RLX or RLX-derived drugs may be used to treat allergic and peripheral vascular diseases, the Bani finding (that RLX reduces respiratory abnormalities in guinea pigs and promotes dilation of alveolar blood capillaries and reduces the thickness of the air-blood barrier, thereby providing evidence for an anti asthmatic property of RLX), still only leads Bani to regard the results as raising the possibility of new therapeutic strategies for allergic asthma in humans.

At the outset, given the concept that asthma is a species of a Th2-dominated disease genus, it is clear that the instant invention concerns treating asthma in human beings, not in rats (Masini) or guinea pigs (Bani).

Masini only indicates that RLX acts by causing endogenous NO production to inhibit histamine release, in rat cell based tests, and it is only on the basis of NO production that RLX is thought to raise the possibility of use to treat allergic diseases.

Such Masini assertion is not motivation to carry out the present invention with an expectation of success (see p. 5 of November 4, 2002 Office Action), but rather a speculative invitation to experiment in the empirical and unpredictable medical arts.

Bani only shows that RLX has an anti asthmatic property in treating ovalbumin pre-sensitized guinea pigs, similarly to Masini, i.e., by endogenous production of NO which has been shown to exert beneficial effects on asthma, and thus likewise it is mainly on the basis of NO production that RLX is thought to raise the possibility of use to treat asthma.

Here, also, such Bani assertion is not motivation to carry out the present invention with an expectation of success (see p. 5 of November 4, 2002 Office Action), but rather a speculative invitation to experiment in the empirical and unpredictable medical arts.

Nothing is said in Masini and/or Bani that teaches that RLX is useful to treat asthma in human beings. At best, despite any Examiner asserted art-based motivation to the skilled artisan to combine these two references, Masini and Bani present the classic

situation that in view of the suggested use of RLX to treat allergic diseases (Masini) and to counteract allergic asthma in guinea pigs (Bani), expressly thought in each of the two references to involve endogenous NO production, it would be obvious to try use of RLX to treat asthma with respect to human beings, in order to determine whether it is effective for human use or not.

An invention must be obvious over the art per se, in the sense of 35 USC 103, without having to try in order to determine whether the result is successful or unsuccessful. There is no art taught equivalency between rat and/or guinea pig based RLX experiments and human based RLX experiments in general, or in particular regard to endogenous NO production, on the one hand, and TH1 cell production as opposed to Th2 cell production, on the other hand.

Indeed, the applied art is based on efforts of appellant herein with co-authors and any personal knowledge of appellant herein may not be imputed to the art. More significant, it is clear from Masini and Bani that the various co-authors therein in reality represent the skilled artisan in this field of endeavor, i.e., the unpredictable medical arts, where empirical tests are required to establish useful advances, and where speculation as to mechanisms of action or possible medical uses cannot be accepted in place of empirical test results.

Thus, these co-authors as skilled artisan do not say that rat derived cell tests (Masini) and guinea pig tests (Bani) teach that RLX is useful to treat asthma in human beings, but rather that the Masini test results of rat cell based dependency of RLX-induced

vasodilation on NO production raises the possibility that RLX or RLX-derived drugs may be used to treat allergic and peripheral vascular diseases, and likewise that the Bani guinea pig test results that RLX reduces respiratory abnormalities and promotes dilation of alveolar blood capillaries and reduces the thickness of the air-blood barrier, provides evidence for an anti asthmatic property of RLX, thus similarly raising the possibility of new therapeutic strategies for allergic asthma in humans.

Point (1) - the Examiner's assertion that guinea pigs per Bani are proper models, thus vitiating the difference between the instant use of RLX to treat human beings and the Bani use of RLX in guinea pig tests, is not well taken.

There is no art basis to equate guinea pig based tests as used in Bani, with human cell based tests as used herein. Indeed, both Bani and Masini constitute the work of individuals who comprise skilled artisans in the unpredictable empirical medical field, as noted above, and who do not state, as the Examiner implies, that guinea pig based tests are equivalent to human cell based tests. Instead, Bani and Masini both premise their results on endogenous NO production, which only raises the possibility that RLX may be useful (or may not be useful) for treating human beings.

Point (2) - The Examiner's assertion that the mechanism by which you get relief of disease is not relevant because it inherently happens, is also not well taken.

It is only because of the Bani and Masini proposed RLX-induced endogenous NO production mechanism of action explanation that the possibility is raised that RLX may be useful to treat human beings, not because of the mechanism of action effect of RLX on any Th2-dominated disease as found per the present invention.

This is not a case where the art shows that human cell based tests indicate that endogenous NO production is found and on the basis of which the possibility is raised that RLX may be useful to treat human beings.

It certainly is not the case where the art shows that human cell based tests indicate asthma to be a Th2-dominated disease, and:

- that it is treatable in human patients by RLX (claim 1), or
- that a pathogenic Th2 response is inhibitable in human patients by RLX to induce endogenous IFN-γ production (claim 2), or
- that development of activated human T cells into Th1-like effectors is stimulatable by RLX to treat a Th2-dominated disease in human patients (claim 3), or
- that a Th2-dominated disease is treatable in human patients by RLX to enhance the Th1 response of the immunological system (claim 4), or
- that a Th2-dominated disease is treatable in human patients by RLX to induce endogenous IFN-γ production (claim 5).

Indeed, such is the basis of the present invention itself.

Point (3) - The Examiner's assertion that the claims fail to distinguish from the referenced patient population, is equally not well taken.

The only relevant patient population at issue herein is the human population, and as earlier indicated, no art established equivalency has been set forth by the Examiner as between guinea pigs and human beings (human patients) to support such assertion.

Point (4) - The Examiner's assertion that scientific reasoning and evidence as a whole indicates that the rejection should be maintained, is likewise not well taken.

The Examiner has not advanced any scientific reasoning or evidence supporting the art rejection. Instead, it is submitted that the art rejection is inferentially premised on an erroneous "at least try" test of obviousness, rather that the true test that the claimed concept must be obvious without having to try to establish whether success or lack of success is the result.

There is no presumption of obviousness under 35 USC 103. Moreover, the results of the invention cannot be appreciated in a technical vacuum, given the implicit unpredictability of action of RLX in the instant empirical medical arts.

As noted in Cronin, cited in appellant's Bigazzi-296, RLX is difficult to recover in pure form, being generally obtained as a crude aqueous extract from sow corpora lutea, and was only recently obtained as highly purified RLX from the ovaries of pregnant pigs, rats, sharks, and the placentas of horses and rabbits, with

partially purified RLX being obtained from cow and human corpora lutea, placentas and decidua (col. 2, lines 15-35).

Per Cronin, mature human RLX exists in the human in the corpora lutea of pregnancy, in the non-pregnant female and in the male (seminal fluid), yet the obtaining of purified RLX preparations from human corpora lutea, placentas and decidua has not yet been demonstrated (col. 1, lines 8-13 and 49-52). Recombinant techniques have been applied to isolation of cDNA clones for rat and porcine RLX, and two human gene forms have been identified by genomic cloning, although only one such gene form, termed H2 relaxin, has been found to be transcribed in corpora lutea (col. 1, lines 53-68).

Cronin states that RLX consists of two peptide chains, referred to as A and B, joined by disulfide bonds with an intra-chain disulfide loop in the A-chain analogous to that of the hormone insulin, the two human RLX genes showing considerable nucleotide and amino acid sequence homology to each other, but with notable regions of sequence divergence, particularly in the amino-terminal region of both A- and B-chains (col. 3, lines 1-8).

Indeed, Cronin notes that the structure of relaxin has apparently diverged considerably among species during evolution, with only 40-48% amino acid sequence homology existing among porcine, rat, shark and human RLX, yet in all species examined, the primary translation product of H2 RLX is a pre prorelaxin consisting of a 25 amino acid signal sequence followed by a B chain of about 29-33 amino acids, a connecting peptide of 104-107 amino

acids (C peptide), and an A chain of 24 amino acids, with the further processing of the pro hormone obtained into RLX being not entirely understood (col. 3, lines 9-26).

Cronin confirms the art designated definition of "relaxin" as generally including polypeptides comprising the amino acid sequence of a naturally occurring (human or non-human animal, such as porcine, murine, etc.) RLX, or comprising an amino acid sequence which differs from such native RLX amino acid sequences by substitutions, deletions, additions and/or modifications of one or more amino acid residues in the A- and/or B-chains of the respective native RLX, as well as glycosylation variants, unglycosylated forms, organic and inorganic salts, and covalently modified derivatives of such native and modified peptides (col. 8, line 6, to col. 9, line 31; and col. 10, line 10, to col. 12, line 36).

Indeed, Cronin emphasizes the unpredictability as to medical uses of RLX in regard to various therapies there discussed, and the confusing results as to given medical uses that have been obtained therewith (col. 4, line 21, to col. 5, line 29; and col. 17, line 38, to col. 18, line 13).

Bigazzi-296, like Cronin, also confirms that the structure of RLX, which is similar to insulin, is different for each species of animals and has been difficult to obtain in pure form (col. 1, lines 9-36), limiting the value of medical use test results therewith (col. 1, lines 37-40; and col. 2, lines 17-41), and emphasizing the unpredictability of its therapeutic use due to its dose-dependency (col. 8, lines 63-67; and col. 9, lines 19-24).

Hence, there is no art supported basis for concluding that tests on animal derived cells such as guinea pig derived cells per Bani or rat derived cells per Masini are equivalent to human derived cells, or that tests using RLX in one cellular environment (animal subjects) are acceptable to establish predictably corresponding use in another cellular environment (human patients).

Clearly, Bani and Masini are not concerned with the instant methods of treating a Th2-dominated disease in a human patient (claims 1, 4 and 5), inhibiting a pathogenic Th2 response in a human patient (claim 2), or stimulating the development of activated human T cells into Th1-like effectors in a human patient (claim 3), let alone the non-elected method of regulating immune homeostasis during pregnancy in a human female patient (claim 6), based on a different mechanism, i.e., stimulation of Th1-like effectors in humans (spec., p. 3, lines 8-19).

Any motivation of the skilled artisan to combine Bani and Masini would still result only in the speculative raising of the possibility that RLX could be used to treat allergic diseases (Masini) or asthma (Bani) in human beings. This is far different from the Examiner's unsupported position that the combination of Bani and Masini teaches in fact that it is obvious in the sense of 35 USC 103 that RLX is usable to treat asthma in human beings.

This unsupported position of obviousness on the part of the Examiner could only occur by impermissible hindsight use of the instant invention itself to show that it is not an invention.

Clearly, appellant was first to recognize RLX use in humans to treat Th2-dominated diseases, based on appellant's recognition that RLX has an inhibiting effect on pathogenic Th2 response.

Bani and Masini have not enriched the medical arts by providing a new method of treating a Th2-dominated disease or pathogenic Th2 response in a human patient, but rather at best alone or in combination present a speculative invitation to experiment to see whether the raised possibility that RLX may be able to treat asthma in human beings is actually correct or incorrect. On the other hand, the invention herein has enriched the medical arts by providing a new and unobvious therapeutic method empirically useful for treating human patients.

This is a situation dealing with an empirical art, with respect to which the court in In re Tomlinson et al., 150 USPQ 623, 626 (1966), stated (in one long paragraph):

> As we see it, appellant's invention is the discovery of what stabilizers for other materials, known in the art, will, and which will not, stabilize polypropylene against degradation by light. The solicitor asserts that one skilled in the art "would expect an[y] ultraviolet light stabilizer for polyethylene to be effective as an ultraviolet stabilizer in polypropylene"....The examiner, with whom the board expressed "total agreement," did not go that far, saying "it would be obvious for a skilled chemist to try to stabilize polypropylene with a known stabilizer for polyethylene," and that it would be

"routine experimentation" for a skilled chemist to attempt to stabilize polypropylene against the deteriorative effect of light by first trying the known stabilizers for polyethylene such as the nickel and cobalt dialkyldithiocarbamates," citing In re Moreton, 48 CCPA 928, 288 F.2d 940, 129 USPQ 288, for the proposition that obviousness does not require absolute predictability. [Emphasis in original.]

Continuing (in that same long paragraph), the court said:

> Our reply to this view is simply that it begs the question, which is obviousness under section 103 of compositions and methods, not of the direction to be taken in making efforts or attempts. Slight reflection suggests, we think, that there is usually an element of "obvious to try" in any research endeavor, that it is not undertaken with complete blindness but rather with some semblance of a chance of success, and that patentability determinations based on that as the test would not only be contrary to statute but result in a marked deterioration of the entire patent system as an incentive to invest in those efforts and attempts which go by the name of "research." [Emphasis in original.]

The court in Tomlinson further noted (p. 627):

> Considering the evidence as a whole, we think it inescapable that we are here dealing with an art that is quite empirical. [Emphasis added.]

Given the unpredictability of results of efforts in the medical field, and the empirical nature of medical experiments and treatments, as confirmed by Cronin and Bigazzi-296 as noted above, even if the skilled artisan were motivated and had expectations of success, the combination of Bani and Masini represents a speculative invitation to experiment to ascertain whether or not RLX is in fact useful to treat asthma in human patients.

The art rejection under 35 USC 103 is unwarranted since it is based on impermissible hindsight inclusion of the instant disclosure (cf., spec., p. 14, lines 1-12) to show that the instant invention is not an invention, and an implicit holding that on the basis of Bani and Masini it would be obvious to try experiments, i.e., the artisan would be motivated to experiment, to ascertain whether or not RLX is useful to treat asthma in human subjects.

It cannot be overemphasized that the Bani and Masini co-authors, as skilled artisans in the empirical (unpredictable) medical arts, do not teach that it would be obvious to use RLX to treat asthma in human patients, but only that, based rat cell and guinea pig tests, involving attendant endogenous NO production, the possibility is raised that RLX may (or may not) be used to treat allergic diseases (Masini) or that new therapeutic strategies may (or may not) arise for allergic asthma in humans.

For the above reasons, the Board is respectfully requested to reverse the Examiner's sole rejection of appealed claims 1-5 under 35 USC 103, and allow such claims.

Respectfully submitted
for Appellant,

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IX - APPENDIX

The claims on appeal are original claims 1-5 as follows:

1. (ORIGINAL) Method of treating a Th2-dominated disease in a human patient exhibiting said disease, comprising administering to the patient an effective amount of relaxin or derivative thereof for relieving said disease.

2. (ORIGINAL) Method of inhibiting a pathogenic Th2 response in a human patient exhibiting said pathogenic Th2 response, comprising administering to the patient an effective amount of relaxin or derivative thereof for inducing endogenous IFN-γ production for inhibiting said pathogenic Th2 response.

3. (ORIGINAL) Method of stimulating the development of activated human T cells into Th1-like effectors for treating a Th2-dominated disease in a human patient exhibiting said disease, comprising administering to the patient an effective amount of relaxin or derivative thereof for stimulating said development.

4. (ORIGINAL) Method of treating a Th2-dominated disease in a human patient exhibiting said disease, comprising administering to the patient an effective amount of relaxin or a derivative thereof for enhancing Th1 response of the immunological system of the patient for relieving said disease.

5. (ORIGINAL) Method of treating a Th2-dominated disease in a human patient exhibiting said disease, comprising administering to the patient an effective amount of relaxin or a derivative thereof for inducing endogenous IFN-γ production for relieving said disease.

The only remaining claim in the case is original claim 6, withdrawn as being directed to a non-elected invention, as follows:

6. (WITHDRAWN) Method of regulating immune homeostasis during pregnancy of a human female patient exhibiting imbalance in immune homeostasis, comprising administering to the patient an effective amount of relaxin or a derivative thereof for regulating said immune homeostasis.